REMARKS

Claims 1, 3-7 and 10-21 are pending. Applicants have amended claims 1, 3, 4, 6, 11 and 14 to address certain informalities. Upon entry of this Amendment, claims 1, 3-7 and 10-21 will still be pending and under examination.

35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 1, 3-7 and 10-21 as failing to comply with the requirements of 35 U.S.C. §112, second paragraph. The Examiner asserts that claim 1 is in improper Markush format, and that claims 1 and 3 contain certain unclear language. In response, applicants have amended these claims to address the Examiner's concerns.

The Examiner also asserted that claim 3 is in improper dependent form for failing to further limit the subject matter of claim 1. In response, applicants respectfully traverse, noting that claim 1 recites "benazepril" which is not recited in claim 3. Thus, claim 3 indeed further limits the subject matter of claim 1.

35 U.S.C. §103

The Examiner rejected claims 1, 3-7 and 10-21 under 35 U.S.C. §103 as allegedly obvious over U.S. Patent No. 6,303,141 ("'141 patent") in view of EP '430.

In response, applicants respectfully traverse.

The claimed system comprises, in relevant part, an ACE inhibitor that is in the form of (i) a dicarboxylic acid that is derivatized to form a diester, or (ii) a monosalt formed with acid(s). This invention unexpectedly overcomes the difficulty of obtaining ACE inhibitors which (i) remain stable with respect to decomposition in a transdermal system and (ii) exhibit outstanding skin permeation.

In support of this position, applicants make the following remarks.

First, in the '141 patent, no *monosalts* of ACE inhibitors are taught or suggested, let alone their improved stability in matrix-controlled transdermal therapeutic systems according to the present invention. This

is also acknowledged by the Examiner in the Office Action: "...US '141... does not specifically teach monosalts as claimed by claim 1."

The same holds true for diesters of ACE-inhibitors. For example, column 1, lines 17 to 24 of US '141 read:

> Like enalapril, the ACE inhibitors ramipril, cilacapril, trandolapril, benazepril or fosinopril are lipophilic drugs of the actual active form of the dicarboxylic acid. As a result of the *esterification of one carboxyl group* of the respective ACE inhibitor in each case, the substance becomes more lipophilic and thereby more favourable for *oral* absorption. The oral bioavailability of *these prodrugs*, however, is always lower than that of captopril. (emphasis added)

The following passages of the '141 patent relate to salt forms of ACE inhibitors:

> Transdermal systems containing an ACE inhibitor are furthermore described in EP-A2-0 439 430 (reservoir TTS) and EP-A2-0 468 875 (matrix TTS), according to EP-A2-0 478 875 silicone elastomers being used as matrix material.
>
> The object of the present invention is to provide a system for the transdermal supply of ACE inhibitors, in particular of ramipril, trandolapril and/or their *therapeutically active salts*, which is *improved compared with the prior art*. (cf. column 1, lines 51 to 58)

Moreover, column 2, lines 24 to 28 state:

> "The ACE inhibitor can be employed here as a *prodrug* or as an *active form*. ... Examples of ACE inhibitors which may be mentioned are ramipril, trandolapril and/or their active forms (*acid forms*) and also their therapeutically active salts." (emphasis added)

The '141 patent contains no definition as to the nature of these salts. It is, therefore, applicants' position that only in hindsight would one of ordinary skill in the art have read these "therapeutically active salts" as monosalts.

Further, applicants note that the '141 patent stresses improving the transdermal supply of ACE inhibitors, in particular of ramipril, trandolapril and/or their therapeutically active salts, compared with the prior art. This is evident from column 1, lines 55 to 58, cited above. Therefore, applicants maintain that the term "therapeutically active salts" must be interpreted in view of the prior art, e.g. EP '430.

As for EP '430, this reference discloses ACE inhibitors in their active dicarboxylic acid form or as disalts. For instance, page 2, line 55 to page 3, line 1 of EP '430 clearly discloses the dicarboxylic acid forms of benazeprilat and libenzapril with their respective systematic names. Concerning salt forms, EP '430 teaches the use of the stoichiometric salt of the respective compounds (see, page 3, lines 4-5) . EP '430 therefore clearly teaches disalts with regard to the respective ACE inhibitors, since the stoichiometric salt of a dicarboxylic acid is necessarily its disalt.

This teaching is reinforced at page 3, lines 9 to 10, where the salt is referred to as the dicarboxylate, such as maleate (also cited by the Examiner) and by Example 1, where only disalts of the respective ACE inhibitors are mentioned (namely libenzapril dihydrochloride, libenzapril dihydrobromide, benazeprilat dilithium salt and benazeprilat dipotassium salt; see, first column of Tables on pages 5 and 6 of EP '430).

Thus, it is readily apparent that EP '430 fails to teach or suggest monosalts of ACE inhibitors.

In the Office Action, however, the Examiner states at page 5, first full paragraph:

> Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide transdermal system for delivery of salts of ACE inhibitors as disclosed by US '141, and replace the salt of ACE inhibitor by monosalts as disclosed by EP '430, motivated by the teaching of EP '430 that transdermal system that having monosalts ACE inhibitors [sic] showed improved flux through the skin, with reasonable expectation of having transdermal system for delivery of monosalts of ACE inhibitors at improved flux rates.

For the reasons outlined above, applicant traverses this view as erroneous. In fact, at page 7, line 1 to 2, EP '430 states:

> As is readily apparent, the [stoichiometric] salt form of the zwitterionic substance [disalts of ACE inhibitors] is generally more soluble than the free zwitterion in the solvent with the one exception of baclofen methane sulfonate in chloroform. (bracketed language added)

Again, monosalts are not taught or suggested in EP '430.

Finally, in the Office Action, the Examiner asserted that the May 29, 2007 Declaration of Joerg Nink submitted as evidence of non-obviousness had certain experimental shortcomings.

In response, and without conceding the correctness of the Examiner's remarks, applicants submit a second Declaration dated August 21, 2008 and signed by Joerg Nink of Hexal AG. The enclosed Declaration addresses the Examiner's concerns as to experimental design. Specifically, the August 21, 2008 Declaration clearly shows the unexpectedly superior stability of trandolpril diester over its monoester counterpart. As the instant claims encompass systems having diester ACE inhibitors as one embodiment, this Declaration is clear evidence of the claimed system's non-obviousness.

Applicants again maintain that the cited references fail to create a reasonable expectation of success regarding the unexpected properties of the claimed system, particularly in view of the submitted Declaration.

For the above reasons, applicants maintain that the claimed invention is not obvious.

If any additional fees or charges are required at this time, they may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

Respectfully submitted,
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